CLAIM LISTING

Amendments to the claims are reflected in the following listing, which replaces any and all prior versions and listings of claims in the above-referenced application:

1. (Withdrawn) A method of making an implement for use with treatment or analysis of a liquid, comprising:

a) devising a set of heuristic rules from the behavior of the liquid on a scale of the scale of the instrument to be made,

b) fabricating as a part of the instrument a liquid contacting device based upon at least one of the heuristic rules, and

c) providing a means of determination of a characteristic of the liquid based on the liquids behavior in contact with the liquid contacting device.

2. (Cancelled)

3. (Withdrawn) The method according to claim 1, wherein the liquid comprises a suspension of cells, devising the heuristic rules including determining parameters of the liquid contact device effecting lysis of the cells, and implementing selected values of the parameters to provide the desired presence or absence of lysis of cells.

4. (Withdrawn) The method according to claim 3, wherein the liquid is blood, the cells are blood cells suspended in plasma, the parameters include cell stress and cell stress duration.

5. (Withdrawn) The method according to claim 4, wherein the blood cells are red blood cells.

6. (Withdrawn) The method according to claim 5, wherein cell stress is determined as a function of the size of a filtration opening that is sized to prevent red blood cell

passage and cell stress duration is determined as a function of length of a plasma path along a passage leading plasma from the filtration opening.

7. - 12. (Cancelled)

13. (Withdrawn) A blood separation instrument comprising an input opening to an input location for receiving whole blood, a first blood flow channel communicating with the input opening and being of a size to cause blood flow therein from the input location by capillary action, a filter opening into a side of the blood flow channel, the filter having at least one opening therethrough smaller than a red blood cell, a blood plasma collection location for receiving plasma from the filter, an expanded blood flow channel in communication with the first blood flow' channel and having defined therein a plurality of parallel connected channels sized to draw blood therethrough by capillary action.

14. (Withdrawn) The blood separation instrument according to claim 13, wherein the filter comprises a weir formed at the side of the blood flow channel, the weir constricting a slit-like opening through the side of the blood flow channel to a height less than the height of the blood flow channel.

15. (Withdrawn) The blood separation instrument according to claim 13, further comprising a blood plasma flow channel in communication with the slit and of a size to draw plasma through the slit by capillary action.

16. (Withdrawn) The blood separation instrument according to claim 15, wherein the length of the plasma flow channel is sufficiently short as to shorten time of plasma flow therein below a duration such as ordinarily causes lysis of red blood cells

adhered to a slit-like opening the size of the slit-like opening through the side of the blood flow channel.

17. (Withdrawn) An instrument for monitoring capillary pressure including:

a) an entrapped gas encapsulation,

b) a path of liquid flow of a cross-section that causes capillary action motivated flow of the liquid therein,

c) a tube in communication between the encapsulation and the path of liquid flow,

d) the tube having a diameter such that, under capillary pressure of a liquid moving in the path of liquid flow, capillary pressure in the liquid is indicated by a column of the liquid in the tube acting against and compressing the gas in the encapsulation, and

e) the tube being sufficiently transparent or translucent as to allow the meniscus level of the liquid therein to be detected.

18. (Withdrawn) The instrument according to claim 17, wherein the entrapped gas is air.

19. (Withdrawn) The instrument according to claim 17, wherein a cross-sectional dimension of the path is about 20 Am or less.

20. (Withdrawn) The instrument according to claim 17, further comprising a filter pore constricting an input opening from the path into the tube.

21. (Withdrawn) A liquid flow meter including the instrument of claim 17 and having a further instrument for monitoring capillary pressure spaced along the path of liquid flow.

22. (Withdrawn) A method of illuminating a substantially clear liquid specimen for observation comprising:

a) providing a substrate,

b) providing an at least partially light transmitting layer on the substrate to form a specimen support surface and having an interface with the substrate,

c) placing the liquid specimen on the specimen support surface, and

d) illuminating the specimen by:

i) directing light onto the specimen support surface at an angle selected to cause partial reflection at the specimen support surface to divide illuminating light into refracted light and reflected light,

ii) reflecting the refracted light from the substrate at the interface of the layer and the substrate and through the layer to cause visible interference with reflected light that is reflected from the specimen support surface.

23. (Withdrawn) The method according to claim 22, wherein step (b) comprises providing an oxide layer on the substrate.

24. (Withdrawn) The method according to 22, wherein step (a) comprises providing a Si substrate, and step (b) comprises providing a SiO_2 layer on the Si substrate.

25. (Withdrawn) The method according to claim 22, wherein step (b) comprises providing a thin layer in light interference effecting relation to the substrate.

26. (Withdrawn) A liquid specimen handling device, including:

a) a substrate,

b) a layer of at least partially light-transmitting material on the substrate and forming an interface therewith and having an upper specimen support surface, and

c) illumination means mounted to direct light into the specimen at an angle causing partial reflection at the specimen support surface, to divide illuminating light into refracted light and reflected light, and to cause interfering intersection of the refracted light reflected from the substrate-layer interface and the reflected light from the specimen-support surface.

27. (Withdrawn) The device according to claim 26, wherein the layer is an oxide of the material of the substrate.

28. (Withdrawn) The device according to claim 27, wherein the substrate is Si and the layer is SiO_2.

29. (Withdrawn) A liquid specimen test device comprising:

a) a plurality of liquid flow channels defined in a substrate,

b) a plurality of filter openings communicating between the liquid flow channels and a plurality of filtrate collection regions,

c) at least one liquid input reservoir connected in liquid communication with the flow channels,

d) a plurality of expanded output flow channels downstream of the liquid flow channels,

e) a closure covering the flow channels, the filters, the collection regions and the expanded output flow channels, and

f) at least one vent line connecting the collection regions and the expanded flow channels to at least one opening to atmosphere.

30. (Withdrawn) The device according to claim 29, further comprising at least one liquid input opening through the closure to the liquid input reservoir for the input of a liquid test specimen.

31. (Withdrawn) The device according to claim 29, wherein the expanded output flow channels contain multiple capillary flow paths for drawing liquid of a specimen along the paths by capillary action.

32. (Withdrawn) The device according to claim 29, wherein the filter openings comprise weir-type filters opening into the liquid flow channels.

33. (Withdrawn) The device according to claim 32, wherein the liquid flow channels have plural weir-style filters opening thereto and leading to separate filtrate collection regions.

34. (Withdrawn) The device according to claim 33, wherein the substrate is a semiconductor substrate and the closure comprises a glass lid secured thereto.

35. (Withdrawn) The device according to claim 35, wherein the flow channels comprise at least eight flow channels, each of the channels having a filter opening thereto and each flow channel leading to one of at least eight expanded output flow regions.

36. (Withdrawn) The device according to claim 31, wherein the capillary flow paths in the expanded output flow channels are connected in parallel to an associated flow channel.

37. (Withdrawn) The device according to claim 36, wherein the parallel capillary flow paths are serpentine.

38. (Withdrawn) The device according to claim 36, wherein the substrate is a semiconductor chip formed from a single semiconductor crystal wafer.

39. (Withdrawn) The device according to claim 38, wherein the semiconductor crystal is Si.

40. (Withdrawn) The device according to claim 39, in which the liquid flow channel cross-sectional dimensions are sized to effect movement of liquid of a liquid specimen therein by capillary action.

41. (Withdrawn) The device according to claim 40, wherein the liquid flow channel has a cross-section dimension a, where:

$$0.3 > a > 0.1\ \mu m$$

42. (Withdrawn) The device according to claim 41, wherein the crosssectional dimension a is about 0.5 μm.

43. (Withdrawn) A method of cell lysis comprising:

a) moving a liquid suspension of cells in a flow path by capillary action,

b) providing a filter opening into the flow path, the filter having one or more pores sized to engage and retain cells in the suspension and having a length in the direction of liquid flow through the filter sufficiently long to cause lysis of at least some retained cells in the suspension as a function of the stress on the cell and the duration of its retention at the filter pore.

44. (Withdrawn) The method according to claim 43, wherein step (a) comprises moving blood in the flow path, and step (b) comprises providing a filter having one or more pores of a size and length sufficient to cause lysis of at least a portion of the red blood cells in the blood.

45. (Withdrawn) The method according to claim 43, further comprising moving lysed cells and liquid out of the filter through a channel by capillary action to a collection region.

46. (Withdrawn) The method according to claim 44, further comprising moving the lysed red blood cells and plasma from the filter along a channel by capillary action to a collection region.

47. (Withdrawn) The method according to claim 43, wherein step (a) further comprises moving the liquid suspension past the filter to an expanded channel having multiple paths for moving the liquid suspension therein by capillary action.

48. (Withdrawn) The method according to claim 43, wherein step (b) further comprises providing a plurality of filters of varying filter pore geometries along the length of the flow path to effect high and lower rates of lysis at the filters.

49. (Withdrawn) The method according to claim 48, further comprising using the lysis observed as an indicator of Sickle Cell Anemia.

50. (Withdrawn) The method according to claim 48, wherein providing a plurality of filters comprises providing a plurality of filters of differing pore lengths.

51. (Withdrawn) The method according to claim 48, wherein providing a plurality of filters comprises providing a plurality of filters of differing pore widths.

52. (Withdrawn) The method according to claim 48, wherein providing a plurality of filters comprises providing a plurality of filters of varying pore heights.

53. (Withdrawn) A method of fabricating a passive, liquid specimen handing device including:

a) providing a semiconductor substrate;

b) applying a photoresist to the substrate;

c) providing a mask defining liquid flow channels of cross-sectional dimensions suitable to induce capillary action flowing of the liquid therein;

d) exposing the photoresist to U.V. light through the mask;

e) removing the photoresist in locations exposed to light through the mask;

f) etching the semiconductor in areas revealed by removing the photoresist to form the liquid flow channels and other features of the device; and

g) securing a closure layer to the semiconductor substrate over the etched channels and other features of the device.

54. (Withdrawn) The method according to claim 53, wherein the closure layer is glass and step (g) comprises anodic bonding the glass closure layer to the semiconductor substrate.

55. (Withdrawn) The method according to claim 54, wherein the semiconductor is Si.

56. (Withdrawn) the method according to claim 53, wherein step comprises providing a mask defining a liquid flow channel sized to induce capillary action in the liquid of an intended specimen type and having an expanded downstream channel section in communication with the liquid flow channel and with a plurality of parallel connected liquid flow paths therein each of a cross-sectional dimension to induce parallel capillary action flow of the liquid.

57. (Withdrawn) The method according to claim 56, further comprising separately from steps (c), (d), (e) and (f), conducting the steps of applying a photoresist, providing a mask defining filter pores to be etched into the semiconductor surface, exposing the photoresist to U.V. light through the mask, removing the photoresist in

filter pore areas exposed through the mask, and etching the pore areas of the semiconductor substrate to a lesser depth than a preselected depth of the flow channels.

58. (Withdrawn) A micro-engineered blood separation device including:

a) a substrate,

b) a cover plate,

c) a blood inlet reservoir,

d) a blood outlet reservoir,

e) a blood flow channel etched into the substrate and connecting the blood inlet reservoir and the blood outlet reservoir,

f) an area of microfilter etched into the surface, pores of the microfilter having an opening into the blood flow channel, the pores having a cross-sectional dimension less than 10 Am,

g) a plasma outlet channel etched in the surface of the substrate in communication with the pores at ends thereof opposite the ends opening into the blood flow channel, and

h) a plasma outlet reservoir connected with the plasma outlet channel.

59. (Withdrawn) a blood separation instrument comprising:

a) a blood inlet opening;

b) a first reservoir connected with the blood inlet opening;

c) a blood outlet opening;

d) a second reservoir connected with the blood outlet opening;

e) a blood flow path from the first to the second reservoir;

f) a plurality of micro-channel blood filters communicating with the channel between the first and second reservoirs;

g) each of the micro-channel blood filters comprising:

(i) a plurality of micro-channels having at least one cross-sectional dimension less than 1.0 pm in communication with the channel; and

h) the length of the micro-channel of each filter differing in length from the length of the micro-channels of each other filter.

60. (Withdrawn) A method of measuring % hematocrit of a blood specimen including:

a) providing a substrate having a blood flow channel thereon leading away from an input region and having a serpentine path to a vented location,

b) The blood flow channel being of a cross-dimensional size to effect flow of the blood sample by capillary action therein,

c) Introducing a blood specimen to the input region; and

d) Determining how far along the blood flow channel the blood from the specimen flows by capillary action as a function of % hematocrit.

61. (Withdrawn) A % hematocrit testing device for use with a blood specimen including:

a) a substrate;

b) an input region,

c) a blood flow channel formed in the substrate and communicating with the input region,

d) the blood flow channel being of a cross-sectional dimension that will effect blood flow by capillary action,

e) a vent opening to the blood flow channel remote from the input region, whereby the distance along the blood flow channel that blood from a specimen travels from the input region is a function of the % hematocrit of the blood of the specimen.

62. (Withdrawn) The hematocrit testing device of claim 61, wherein a portion of the blood flow channel intermediate the input region and the vent is of serpentine configuration.

63. (Withdrawn) The hematocrit testing device of claim 61, further comprising flow-slowing chambers formed in the substrate in the path of blood flow in the blood flow channel.

64. (Withdrawn) A method of designing a device including:

a) operational modeling the device by applying known relationships of theoretical operations features of the device to define a design space,

b) fashioning the actual operational features of the device from within the constrained design space.

65. – 68. (Cancelled)

69. (Withdrawn) The instrument according to claim 65, wherein the instrument is configured for blood, the first passage being of a size to cause blood flow by capillary action, the filter having at least one opening therethrough smaller than a chosen constituent element, the expanded flow channel comprising a plurality of parallel connected channels sized to draw blood therethrough by capillary action.

70. (Withdrawn) The instrument according to claim 69, wherein the at least one opening of the filter is sized to block passage of constituent cells therethrough, the size of the at least one opening of the filter and flow rate determining dimensions of the first passage and the plurality of parallel connected channels being chosen to control red blood cell stress and stress duration to control cell lysis.

71. (Withdrawn) The instrument according to claim 69, wherein the at least one opening of the filter is sized to block passage of cells therethrough, the size of the at least one opening of the filter and the flow rate determining dimensions of the first passage and plurality of parallel connected channels being chosen to control cell stress and stress duration to determine the level of red blood cell lysis.

72. – 111. (Cancelled)

112. (New) An instrument for observation, treatment, or analysis of a sample of a liquid comprising:

a liquid input opening for receiving a liquid sample,

a first passage leading from said liquid input opening to an expanded liquid flow region,

at least one filter in fluid communication with said first passage between said liquid input opening and said expanded liquid flow region, and

at least one filtrate channel in fluid communication with said at least one filter, wherein said liquid flow expanded region comprises a plurality of parallel capillary channels sized to sustain a draw of said liquid sample through said first passage tangentially past said at least one filter by capillary action.

113. (New) The instrument according to claim 112, wherein said liquid sample is a complex fluid.

114. (New) The instrument according to claim 112, wherein said draw of said liquid sample through said first passage tangentially past said at least one filter by capillary action filters said liquid sample into at least one filtrate flow in said at least one filtrate channel and the remaining liquid sample flow continuing in said first passage.

115. (New) The instrument according to claim 112, wherein said plurality of parallel capillary channels are sized to sustain a draw of said liquid sample through said first passage for a predetermined amount of time.

116. (New) The instrument according to claim 114, wherein said plurality of parallel capillary channels are sized to produce at least a nanoliter of said at least one filtrate flow from said at least one filter.

117. (New) The instrument according to claim 114, wherein said at least one filtrate channel further comprises a testing location in which at least a portion of said at least one filtrate flow is collected for analysis.

118. (New) The instrument according to claim 117, wherein the analysis of said at least one filtrate flow includes electro-optical analysis.

119. (New) The instrument according to claim 118, wherein the electro-optical analysis comprises a laser, a first reflective sidewall at said testing location positioned to direct laser light from the laser through said test location, a photodetector, and a second reflective sidewall at said testing location positioned to direct laser light from said test location to the photodetector.

120. (New) The instrument according to claim 113, wherein said complex fluid is a biological fluid.

121. (New) The instrument according to claim 120, wherein said biological fluid comprises at least one formed element.

122. (New) The instrument according to claim 121, wherein said at least one filter lyses at least a portion of said at least one formed element.

123. (New) The instrument according to claim 121, wherein said plurality of parallel capillary channels are sized to control the degree of lysing of said at least one formed element.

124. (New) The instrument according to claim 112, wherein each capillary channel of said plurality of parallel capillary channels are about 45 μm wide and at least 10 μm in length.

125. (New) The instrument according to claim 112, wherein said at least one weir filter comprises a channel having width of about 200 μm along the side of said first passage, a height of about 1 μm, and a length of about 30 μm coupling said first passage to said filtrate channel.

126. (New) The instrument according to claim 117, wherein said analysis comprises at least one of an identification of at least one analyte in said at least one filtrate flow, a quantification of the concentration of at least one analyte in said at least one filtrate flow, and an isolation of at least one analyte in said at least one filtrate flow.

127. (New) The instrument according to claim 126, wherein said at least one analyte in said at least one filtrate flow comprises at least one of a protein, an amino acid, an enzyme, an electrolyte, a nucleotide, and a dissolved gasses.

128. (New) The instrument according to claim 112, wherein said expanded liquid flow region comprises a total width from about 0.4 to 2.5 mm and a length of from about 2 to 20 mm.

129. The instrument according to claim 112, wherein said a plurality of parallel capillary channels have a cross-sectional dimension a, where 0.3 μm > a > 0.1 μm.

130. (New) The instrument according to claim 114, wherein said at least one filtrate flow comprises a plasma filtrate.

131. (New) An instrument comprising:

a liquid input opening for receiving a liquid sample,

a first passage leading from said liquid input opening to an expanded liquid flow region comprising a capillary action means for motivating said liquid sample through said first passage,

at least one filter in fluid communication with said first passage between said liquid input opening and said expanded liquid flow region, and

at least one filtrate channel in fluid communication with said at least one filter.